

### **Role of nitric oxide in diabetic nephropathy.**

Prabhakar SS. *Semin Nephrol* 2004;24:333-344.

Diabetic nephropathy is the leading cause of end-stage renal disease in the Western hemisphere. Endothelial dysfunction is the central pathophysiologic denominator for all cardiovascular complications of diabetes including nephropathy. Abnormalities of nitric oxide (NO) production modulate renal structure and function in diabetes but, despite the vast literature, major gaps exist in our understanding in this field because the published studies mostly are confusing and contradictory. In this review, we attempt to review the existing literature, discuss the controversies, and reach some general conclusions as to the role of NO production in the diabetic kidney. The complex metabolic milieu in diabetes triggers several pathophysiologic mechanisms that simultaneously stimulate and suppress NO production. The net effect on renal NO production depends on the mechanisms that prevail in a given stage of the disease. Based on the current evidence, it is reasonable to conclude that early nephropathy in diabetes is associated with increased intrarenal NO production mediated primarily by constitutively released NO (endothelial nitric oxide synthase [eNOS] and neuronal nitric oxide synthase [nNOS]). The enhanced NO production may contribute to hyperfiltration and microalbuminuria that characterizes early diabetic nephropathy. On the other hand, a majority of the studies indicate that advanced nephropathy leading to severe proteinuria, declining renal function, and hypertension is associated with a state of progressive NO deficiency. Several factors including hyperglycemia, advanced glycosylation end products, increased oxidant stress, as well as activation of protein kinase C and transforming growth factor (TGF)-beta contribute to decreased NO production and/or availability. These effects are mediated through multiple mechanisms such as glucose quenching, and inhibition and/or posttranslational modification of NOS activity of both endothelial and inducible isoforms. Finally, genetic polymorphisms of the NOS enzyme also may play a role in the NO abnormalities that contribute to the development and progression of diabetic nephropathy.

### **Coenzyme Q10 and diabetic endotheliopathy: oxidative stress and the 'recoupling hypothesis'.**

Chew GT, Watts GF. *QJM* 2004;97:537-548.

Increased oxidative stress in diabetes mellitus may underlie the development of endothelial cell dysfunction by decreasing the availability of nitric oxide (NO) as well as by activating pro-inflammatory pathways. In the arterial wall, redox imbalance and oxidation of tetrahydrobiopterin (BH(4)) uncouples endothelial nitric oxide synthase (eNOS). This results in decreased production and increased consumption of NO, and generation of free radicals, such as superoxide and peroxynitrite. In the mitochondria, increased redox potential uncouples oxidative phosphorylation, resulting in inhibition of electron transport and increased transfer of electrons to molecular oxygen to form superoxide and other oxidant radicals. Coenzyme Q(10) (CoQ), a potent antioxidant and a critical intermediate of the electron transport chain, may improve endothelial dysfunction by 'recoupling' eNOS and mitochondrial oxidative phosphorylation. CoQ supplementation may also act synergistically with anti-atherogenic agents, such as fibrates and statins, to improve endotheliopathy in diabetes.

### **Folate and homocysteine levels in pregnancy.**

Megahed MA, Taher IM. *Br J Biomed Sci* 2004;61:84-87.

This study aims to determine serum folate and plasma homocysteine levels in healthy pregnant women following a live birth and compare them with healthy non-pregnant women. Fifty healthy gravid multiparous women are included in the study and 25 normal non-pregnant female subjects act as controls (group I). The pregnant women are divided into two groups according to interpregnancy interval: group II (six months or less); group III (18-24 months). Venous blood samples are analysed for red blood cell folate and homocysteine, vitamin B12, serum folate and albumin, and serum aminotransferases (ALT and AST). There was a significant decrease in red cell folate and serum folate in group II compared to the control group ( $P<0.001$ ). Serum vitamin B12 showed no significant difference. Plasma homocysteine and serum albumin showed significant decreases in both groups II and III compared to the control group. ( $P<0.001$ ) There was significant positive correlation between homocysteine and serum albumin in the three studied groups. ( $r=0.42$ ,  $P<0.001$ ;  $r=0.45$ ,  $P<0.001$ ;  $r=0.51$ ,  $P<0.001$ , respectively). There was significant negative correlation between red cell folate and homocysteine in the three studied groups. ( $r=-0.48$ ,  $P<0.001$ ;  $r=-0.53$ ,  $P<0.001$ ;  $r=-0.49$ ,  $P<0.001$ , respectively). Two cases in group II showed signs of intrauterine growth retardation. The results suggest that pregnant females with short interpregnancy intervals are more likely to develop folate deficiency. Educational strategies are required to increase folate awareness among women to promote the benefits of folic acid supplementation. Mandatory folate fortification of foods should be defined and monitored.

### **Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study.**

Weijl NI, Elsendoorn TJ, Lentjes EG, et al. *Eur J Cancer* 2004;40:1713-1723.

Cisplatin-induced toxicities are mainly caused by the formation of free radicals, leading to oxidative organ damage. Plasma concentrations of antioxidants decrease significantly during cisplatin chemotherapy for cancer. Forty-eight cancer patients treated with cisplatin-based chemotherapy were randomised in a double-blind manner to receive either supplementation with vitamin C, vitamin E and selenium dissolved in a beverage or to receive a placebo beverage. Primary outcome measures were the amount of nephrotoxicity and ototoxicity induced by cisplatin. No significant differences were found between the two study groups with respect to these primary outcome measures. However, patients who achieved the highest plasma concentrations of the three antioxidant micronutrients had significantly less loss of high-tone hearing. In addition, significant correlations were found between the reduced/oxidised vitamin C ratio and malondialdehyde (MDA), markers of oxidative stress, and cisplatin-induced ototoxicity and nephrotoxicity. The lack of protection against cisplatin-induced toxicities in patients in the intervention arm may be related to poor compliance and/or inadequate supplementation. Supplementation with a higher dose (intensity) and in combination with other antioxidants should be investigated further.

**Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis.**

Usha PR, Naidu MUR. *Clin Drug Invest* 2004; 24:353-363.

**OBJECTIVE:** Glucosamine, classified as a slow-acting drug in osteoarthritis (SADOA), is an efficacious chondroprotective agent.

Methylsulfonylmethane†(MSM), the isoxidised form of dimethyl-sulfoxide (DSMO), is an effective natural analgesic and anti-inflammatory agent. The aim of this study was to compare the efficacy and safety of oral glucosamine (Glu),

methylsulfonylmethane (MSM), their combination and placebo in osteoarthritis of the knee. **PATIENTS AND DESIGN:** A total of 118 patients of either sex with mild to moderate osteoarthritis were included in the study and randomised to receive either Glu 500mg, MSM 500mg, Glu and MSM or placebo capsules three times daily for 12 weeks. Patients were evaluated at 0 (before drug administration), 2, 4, 8 and 12 weeks post-treatment for efficacy and safety. The efficacy parameters studied were the pain index, the swelling index, visual analogue scale pain intensity, 15m walking time, the Lequesne index, and consumption of rescue medicine. **RESULTS:** Glu, MSM and their combination significantly improved signs and symptoms of osteoarthritis compared with placebo. There was a statistically significant decrease in mean ( $\pm$  SD) pain index from  $1.74 \pm 0.47$  at baseline to  $0.65 \pm 0.71$  at week 12 with Glu ( $p < 0.001$ ). MSM significantly decreased the mean pain index from  $1.53 \pm 0.51$  to  $0.74 \pm 0.65$ , and combination treatment resulted in a more significant decrease in the mean pain index ( $1.7 \pm 0.47$  to  $0.36 \pm 0.33$ ;  $p < 0.001$ ). After 12 weeks, the mean swelling index significantly decreased with Glu and MSM, while the decrease in swelling index with combination therapy was greater ( $1.43 \pm 0.63$  to  $0.14 \pm 0.35$ ;  $p < 0.05$ ) after 12 weeks. The combination produced a statistically significant decrease in the Lequesne index. All treatments were well tolerated. **CONCLUSION:** Glu, MSM and their combination produced an analgesic and anti-inflammatory effect in osteoarthritis. Combination therapy showed better efficacy in

reducing pain and swelling and in improving the functional ability of joints than the individual agents. All the treatments were well tolerated. The onset of analgesic and anti-inflammatory activity was found to be more rapid with the combination than with Glu. It can be concluded that the combination of MSM with Glu provides better and more rapid improvement in patients with osteoarthritis.

**The effects of 'supra-physiological' vitamin B12 administration on temporary threshold shift.**

Quaranta A, Scaringi A, Bartoli R, et al. *Int J Audiol* 2004;43:162-165.

The aim of this study was to evaluate, in 20 young volunteer subjects, the effects of supra-physiological vitamin B12 administration on noise-induced temporary threshold shift (TTS). All subjects had hearing thresholds within 15 dBHL and type A tympanograms. The subjects were randomly assigned to two different groups. Experimental group subjects received cyanocobalamin, 1 mg daily for 7 days, and 5 mg on the eighth day. Control group subjects received a placebo injection daily for 8 days. The vitamin B12 concentration, hearing thresholds and TTS2 (10 min of exposure, narrowband noise centred at 3 kHz, bandwidth of 775 Hz, 112 dB SPL) were measured before and 8 days after treatment. At the end of treatment, the serum vitamin B12 concentration was significantly increased in the experimental group. After 8 days of treatment, the control group showed the same hearing thresholds and TTS2 degrees. Statistical analysis showed that TTS2 decreased significantly at 3 and 4kHz when cobalamin was used to increase the serum concentration of vitamin B12 to  $> 2350$  pg/ml. In addition, a protective effect at 3 kHz in the experimental group was evident when compared with the placebo group. These results suggest that elevated plasma cyanocobalamin levels may reduce the risk of hearing dysfunction resulting from noise exposure in healthy, young subjects.

**Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study.**

Berman M, Erman A, Ben-Gal T, et al. *Clin Cardiol* 2004;27:295-299.

**BACKGROUND:** The number of patients awaiting heart transplantation is increasing in proportion to the waiting period for a donor. Studies have shown that coenzyme Q10 (CoQ10) has a beneficial effect on patients with heart failure. **HYPOTHESIS:** The purpose of the present double-blind, placebo-controlled, randomized study was to assess the effect of CoQ10 on patients with end-stage heart failure and to determine if CoQ10 can improve the pharmacological bridge to heart transplantation. **METHODS:** A prospective double-blind design was used. Thirty-two patients with end-stage heart failure awaiting heart transplantation were randomly allocated to receive either 60 mg U/day of Ultrasome – CoQ10 (special preparation to increase intestinal absorption) or placebo for 3 months. All patients continued their regular medication regimen. Assessments included anamnesis with an extended questionnaire based partially on the Minnesota Living with Heart Failure Questionnaire, 6-min walk test, blood tests for atrial natriuretic factor (ANF) and tumor necrosis factor (TNF), and echocardiography. **RESULTS:** Twenty-seven patients completed the study. The study group showed significant improvement in the 6-min walk test and a decrease in dyspnea, New York Heart Association (NYHA) classification, nocturia, and fatigue. No significant changes were noted after 3 months of treatment in echocardiography parameters (dimensions and contractility of cardiac chambers) or ANF and TNF blood levels. **CONCLUSIONS:** The administration of CoQ10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life. However, there were no objective changes in echo measurements or ANF and TNF blood levels. Coenzyme Q10 may serve as an optional addition to the pharmacologic armamentarium of patients with end-stage heart failure. The apparent discrepancy between significant clinical improvement and unchanged cardiac status requires further investigation.

**Acute *Rhodiola rosea* intake can improve endurance exercise performance.**

De Bock K, Eijnde BO, Ramaekers M, Hespel P. *Int J Sport Nutr Exerc Metab* 2004;14:298-307.

**PURPOSE:** The purpose of this study was to investigate the effect of acute and 4-week *Rhodiola rosea* intake on physical capacity, muscle strength, speed of limb movement, reaction time, and attention. **METHODS:** PHASE I: A double blind placebo-controlled randomized study (n = 24) was performed, consisting of 2 sessions (2 days per session). Day 1: One hour after acute *Rhodiola rosea* intake (R, 200-mg *Rhodiola rosea* extract containing 3% rosavin + 1% salidroside plus 500 mg starch) or placebo (P, 700 mg starch) speed of limb movement (plate tapping test), aural and visual reaction time, and the ability to sustain attention (Fepsy Vigilance test) were assessed. Day 2: Following the same intake procedure as on day 1, maximal isometric knee-extension torque and endurance exercise capacity were tested. Following a 5-day washout period, the experimental procedure was repeated, with the treatment regimens being switched between groups (session 2). PHASE II: A double blind placebo-controlled study (n = 12) was performed. Subjects underwent sessions 3 and 4, identical to Phase I, separated by a 4-week R/P intake, during which subjects ingested 200 mg R/P per day. **RESULTS:** PHASE I: Compared with P, acute R intake in Phase I increased (p < .05) time to exhaustion from 16.8 +/- 0.7 min to 17.2 +/- 0.8 min. Accordingly, VO<sub>2</sub> peak (p < .05) and VCO<sub>2</sub> peak (p < .05) increased during R compared to P from 50.9 +/- 1.8 ml x min<sup>-1</sup> x kg<sup>-1</sup> to 52.9 +/- 2.7 ml x min<sup>-1</sup> x kg<sup>-1</sup> (VO<sub>2</sub>peak) and from 60.0 +/- 2.3 ml x min<sup>-1</sup> x kg<sup>-1</sup> to 63.5 +/- 2.7 ml x min<sup>-1</sup> x kg<sup>-1</sup> (VCO<sub>2</sub>peak). Pulmonary ventilation (p = .07) tended to increase more during R than during P (P: 115.9 +/- 7.7 L/min; R: 124.8 +/- 7.7 L/min). All other parameters remained unchanged. PHASE II: Four-week R intake did not alter any of the variables measured. **CONCLUSION:** Acute *Rhodiola rosea* intake can improve endurance exercise capacity in young healthy volunteers. This response was not altered by prior daily 4-week *Rhodiola* intake.

### **Plasma lipid parameters in patients with alcoholic fatty liver after treatment with essential phospholipids.**

Turecky L, Kupcova V, Szantova M, Uhlikova E. *Bratisl Lek Listy* 2003;104:227-231.

**BACKGROUND:** Fatty liver is the earliest and most common response to alcohol. The accumulation of lipid particles in hepatocytes alters the ultrastructure of cellular membranes. The purpose of our study was to investigate the effect of the administration of essential phospholipids on plasma lipid parameters in patients with alcoholic fatty liver. **METHODS:** Our open clinical trial was performed in patients suffering from alcoholic fatty liver. The investigated group consisted of 29 patients. Two capsules of Essentiale forte were administered 3 times daily for 3 months. Individual biochemical parameters were examined each month. Values of total cholesterol, HDL- and LDL-cholesterol, triacylglycerols, apoprotein A and B were determined. **RESULTS:** The therapy with essential phospholipids had positive effects on the parameters of hepatocyte integrity. The levels of total cholesterol, triacylglycerols and apoprotein B were significantly higher in patients with fatty liver than in the controls. The concentration of HDL-cholesterol was also higher before the therapy than in the control group. There was no difference in levels of apoprotein A and LDL-cholesterol between the patients and the controls. There was no significant therapeutic effect on plasma lipid parameters in the group of patients with fatty liver. **CONCLUSIONS:** The effects of treatment of alcoholic fatty liver with essential phospholipids were studied. The therapy had positive effects on the parameters of hepatocyte integrity. There was no significant therapeutic effect of the therapy on plasma lipid parameters.

### **An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort.**

Jatoi A, Rowland K, Loprinzi CL, et al. *J Clin Oncol* 2004;22:2469-2476.

**PURPOSE:** Studies suggest eicosapentaenoic acid (EPA), an omega-3 fatty acid, augments weight, appetite, and survival in cancer-associated wasting. This study determined whether an EPA supplement-administered alone or with megestrol acetate (MA)-was more effective than MA. **PATIENTS AND METHODS:** Four hundred twenty-one assessable patients with cancer-associated wasting were randomly assigned to an EPA supplement 1.09 g administered bid plus placebo; MA liquid suspension 600 mg/d plus an isocaloric, isonitrogenous supplement administered twice a day; or both. Eligible patients reported a 5-lb, 2-month weight loss and/or intake of less than 20 calories/kg/d. **RESULTS:** A smaller percentage taking the EPA supplement gained  $\geq 10\%$  of baseline weight compared with those taking MA: 6% v 18%, respectively ( $P = .004$ ). Combination therapy resulted in weight gain of  $\geq 10\%$  in 11% of patients ( $P = .17$  across all arms). The percentage of patients with appetite improvement (North Central Cancer Treatment Group Questionnaire) was not statistically different: 63%, 69%, and 66%, in EPA-, MA-, and combination-treated arms, respectively ( $P = .69$ ). In contrast, 4-week Functional Assessment of Anorexia/Cachexia Therapy scores suggested MA-containing arms experienced superior appetite stimulation compared with the EPA arm, with scores of 40, 55, and 55 in EPA-, MA-, and combination-treated arms, respectively ( $P = .004$ ). Survival was not significantly different among arms. Global quality of life was not significantly different among groups. With the exception of increased impotence in MA-treated patients, toxicity was comparable. **CONCLUSION:** This EPA supplement, either alone or in combination with MA, does not improve weight or appetite better than MA alone.

### **Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density.**

Abreu MT, Kantorovich V, Vasiliauskas EA, et al. *Gut* 2004;53:1129-1136.

**OBJECTIVES:** Many patients with Crohn's disease (CD) have low bone mineral density (BMD) that may not be solely attributable to glucocorticoid use. We hypothesised that low BMD in patients with CD is associated with elevated circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH)(2)D). We further hypothesised that this was secondary to increased synthesis of 1,25(OH)(2)D by inflammatory cells in the intestine. The aim of this study was to examine the relationship between 1,25(OH)(2)D levels and BMD in patients with CD. **METHODS:** An IRB approved retrospective review of medical records from patients with CD (n = 138) or ulcerative colitis (UC, n = 29). Measurements of vitamin D metabolites and immunoreactive parathyroid hormone (iPTH) were carried out. BMD results were available for 88 CD and 20 UC patients. Immunohistochemistry or real time reverse transcription-polymerase chain reaction (RT-PCR) for the enzyme 1 $\alpha$ -hydroxylase was performed on colonic biopsies from patients with CD (14) or UC (12) and normal colons (4). **RESULTS:** Inappropriately high levels of serum 1,25(OH)(2)D (>60 pg/ml) were observed in 42% of patients with CD compared with only 7% in UC, despite no differences in mean iPTH. Serum 1,25(OH)(2)D levels were higher in CD (57 pg/ml) versus UC (41 pg/ml) (p = 0.0001). In patients with CD, there was a negative correlation between 1,25(OH)(2)D levels and lumbar BMD (r = -0.301, p = 0.005) independent of therapeutic glucocorticoid use. 1,25(OH)(2)D levels also correlated with CD activity. Lastly, immunohistochemistry and RT-PCR demonstrated increased expression of intestinal 1 $\alpha$ -hydroxylase in patients with CD. **CONCLUSIONS:** These data demonstrate that elevated 1,25(OH)(2)D is more common in CD than previously appreciated and is independently associated with low bone mineral

density. The source of the active vitamin D may be the inflamed intestine. Treatment of the underlying inflammation may improve metabolic bone disease in this subgroup of patients.

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### **Microcirculatory efficacy of topical treatment with aescin plus essential phospholipids gel in venous insufficiency and hypertension: new clinical observations.**

Belcaro G, Cesarone MR, Dugall M. *Angiology* 2004;55:S1-S5.

Aescin plus essential phospholipids (AEPL) topical gels are used for local treatment of venous and microcirculatory alterations (varicose veins, chronic venous insufficiency). Bruises, swelling, thrombophlebitis, and contusions are effectively treated with AEPL. Active ingredients are escinate and essential phospholipids (EPL). The aim of this new study was the evaluation of the efficacy of the effects of AEPL gel on the microcirculation in subjects with chronic venous insufficiency, venous hypertension (CVH), and venous microangiopathy. Patients were assessed measuring skin flux with laser-Doppler flowmetry (LDF). After 2 weeks of local treatment, all individual values (100%) were significantly decreased (p < 0.05), indicating an improvement in the microcirculation. In all treated patients, flux decreased at least 30% (indicating a decrease in the level of venous microangiopathy) (p < 0.05). Considering these observations, topical treatment with AEPL in areas of venous microangiopathy is beneficial, can prevent ulceration, and improves the skin healing processes.

### **Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke.**

Rundek T, Naini A, Sacco R, et al.  
*Arch Neurol* 2004;61:889-892.

**BACKGROUND:** Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are widely used for the treatment of hypercholesterolemia and coronary heart disease and for the prevention of stroke. There have been various adverse effects, most commonly affecting muscle and ranging from myalgia to rhabdomyolysis. These adverse effects may be due to a coenzyme Q(10) (CoQ(10)) deficiency because inhibition of cholesterol biosynthesis also inhibits the synthesis of CoQ(10). **OBJECTIVE:** To measure CoQ(10) levels in blood from hypercholesterolemic subjects before and after exposure to atorvastatin calcium, 80 mg/d, for 14 and 30 days. **DESIGN:** Prospective blinded study of the effects of short-term exposure to atorvastatin on blood levels of CoQ(10). **SETTING:** Stroke center at an academic tertiary care hospital. **PATIENTS:** We examined a cohort of 34 subjects eligible for statin treatment according to National Cholesterol Education Program: Adult Treatment Panel III criteria. **RESULTS:** The mean  $\pm$  SD blood concentration of CoQ(10) was 1.26  $\pm$  0.47 micro g/mL at baseline, and decreased to 0.62  $\pm$  0.39 micro g/mL after 30 days of atorvastatin therapy ( $P < .001$ ). A significant decrease was already detectable after 14 days of treatment ( $P < .001$ ). **CONCLUSIONS:** Even brief exposure to atorvastatin causes a marked decrease in blood CoQ(10) concentration. Widespread inhibition of CoQ(10) synthesis could explain the most commonly reported adverse effects of statins, especially exercise intolerance, myalgia, and myoglobinuria.

### **Topical vitamin B12 – a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial.**

Stucker M, Pieck C, Stoerb C, et al.  
*Br J Dermatol* 2004;150:977-983.

**BACKGROUND:** Vitamin B(12) is an effective scavenger of nitric oxide (NO). As the experimental application of a NO synthase inhibitor, N omega-nitro-L-arginine, led to a clear decrease in pruritus and erythema in atopic dermatitis, it would be reasonable to assume a comparable effect of vitamin B(12). **OBJECTIVES:** The efficacy and tolerability of a new vitamin B(12) cream as a possible alternative to current therapies was examined. **METHODS:** A prospective, randomized and placebo-controlled phase III multicentre trial, involving 49 patients was conducted. For the treatment duration of 8 weeks, each patient applied twice daily (in the morning and evening) the vitamin B(12)-containing active preparation to the affected skin areas of one side of the body and the placebo preparation to the contralateral side according to the randomization scheme. **RESULTS:** On the body side treated with the vitamin B(12) cream, the modified Six Area Six Sign Atopic Dermatitis score dropped to a significantly greater extent than on the placebo-treated body side (for the investigational drug 55.34  $\pm$  5.74 SEM, for placebo 28.87  $\pm$  4.86 SEM,  $P < 0.001$ ). At the conclusion of the study, the investigator and patients awarded mostly a 'good' or 'very good' rating to the active drug (58% and 59%, respectively) and a 'moderate' or 'poor' rating to the placebo (89% and 87%, respectively). **CONCLUSIONS:** Topical vitamin B(12) is a new therapeutic approach in atopic dermatitis. These results document a significant superiority of vitamin B(12) cream in comparison with placebo with regard to the reduction of the extent and severity of atopic dermatitis. Furthermore, the treatment was very well tolerated and involved only very low safety risks for the patients.

### Effect of vitamin E supplementation on vitamin K status in adults with normal coagulation status.

Booth SL, Golly I, Satchek JM, et al. *Am J Clin Nutr* 2004;80:143-148.

**BACKGROUND:** Cases of enhanced anticoagulant effect in response to high-dose vitamin E supplementation have been reported among patients taking oral anticoagulants. Although a vitamin E-vitamin K interaction was proposed to underlie this effect, it has not been systematically investigated in adults with normal baseline coagulation status. **OBJECTIVE:** The objective was to study the effect of 12 wk of supplementation with 1000 IU RRR-alpha-tocopherol/d on biochemical measures of vitamin K status in men and women not taking oral anticoagulants. **DESIGN:** Vitamin K status, which was assessed with the use of plasma phylloquinone concentrations, the degree of under-gamma-carboxylation of prothrombin (proteins induced by vitamin K absence-factor II, PIVKA-II), and the percentage of undercarboxylated osteocalcin (ucOC), was determined in 38 men and women with rheumatoid arthritis (study A) and in 32 healthy men (study B) participating in 2 independent, 12-wk randomized clinical trials of vitamin E supplementation (1000 IU/d). **RESULTS:** Mean (+/- SD) PIVKA-II increased from 1.7 +/- 1.7 to 11.9 +/- 16.1 ng/mL ( $P < 0.001$ ) in study A and from 1.8 +/- 0.6 to 5.3 +/- 3.9 ng/mL ( $P < 0.001$ ) in study B in response to 12 wk of vitamin E supplementation. An increase in PIVKA-II is indicative of poor vitamin K status. In contrast, the other measures of vitamin K status (ie, plasma phylloquinone concentration and percentage of ucOC) did not change significantly in response to the supplementation. **CONCLUSIONS:** High-dose vitamin E supplementation increased PIVKA-II in adults not receiving oral anticoagulant therapy. The clinical significance of these changes warrants further investigation, but high doses of vitamin E may antagonize vitamin K. Whether such an interaction is potentially beneficial or harmful remains to be determined.

### Red wine polyphenols prevent cardiovascular alterations in L-NAME-induced hypertension.

Pechanova O, Bernatova I I, Babal P, et al. *J Hypertens* 2004;22:1551-1559.

**OBJECTIVE:** Red wine polyphenols have been reported to possess beneficial properties for preventing cardiovascular diseases but their effects on hemodynamic and functional cardiovascular changes during inhibition of nitric oxide (NO) synthesis have not been elucidated. **DESIGN:** The effects of the red wine polyphenols, Provinols, on arterial hypertension as well as left ventricular (LV) hypertrophy, myocardial fibrosis and vascular remodeling were investigated in rats during chronic inhibition of nitric oxide synthase (NOS) activity. Rats were divided into four groups: a control group, a group treated with N-nitro-L-arginine methyl ester (L-NAME) (40 mg/kg per day), a group receiving Provinols (40 mg/kg per day) alone or Provinols plus L-NAME. **RESULTS:** Provinols markedly reduced the increase in both blood pressure and protein synthesis in the heart and aorta caused by chronic inhibition of NO synthesis. Provinols reduced myocardial fibrosis even though it did not affect LV hypertrophy. In addition, Provinols prevented aortic thickening and corrected the augmented reactivity of the aorta to norepinephrine and the attenuated endothelium-dependent relaxation to acetylcholine in NO-deficient rats. These alterations were associated with an increase of NOS activity, a moderate enhancement of endothelial NOS expression and a reduction of oxidative stress in the LV and aorta. **CONCLUSION:** Our results provide evidence that Provinols partially prevents L-NAME-induced hypertension, cardiovascular remodeling and vascular dysfunction via the increase of NO-synthase activity and prevention of oxidative stress. Thus, the beneficial effects of plant polyphenols in prevention of hypertension may result from their complex influence on the NO balance in the cardiovascular system.

### Effect of Radix notoginseng saponins on platelet activating molecule expression and aggregation in patients with blood hyperviscosity syndrome.

Wang J, Xu J, Zhong JB. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2004;24:312-316. [Article in Chinese]

**OBJECTIVE:** In order to explore the relationship between the active components and the functional links of Chinese herbs, the effect of Xuesaitong capsule, a preparation made of multi-component Panax notoginseng saponins (PNS) on platelet activating molecule expression and aggregation in patients with blood hyperviscosity syndrome (BHS) was observed, with aspirin (ASP) as a control. **METHODS:** One hundred and twenty patients with BHS were divided, adopting randomized, double-blinded and double simulated principle into 2 groups, the PNS group and the ASP group, 60 in each group. Changes of the TCM clinical syndrome, platelet adhesion and aggregation, endothelin (ET), prostacyclin, thromboxane, CD62P and CD41 before treatment and after 28 days treatment were observed. **RESULTS:** Comparison between the therapeutic effects of the two groups on TCM clinical syndrome showed that the total effective rate in the PNS group was 86.67% and that in the ASP group 56.67%, showing significant difference ( $P < 0.05$ ). Compared with before treatment, after treatment, levels of platelet adhesion and aggregation, endothelin, prostacyclin and thromboxane were significantly different in both groups ( $P < 0.05$  or  $P < 0.01$ ); levels of CD62P and CD41 in the PNS group were also significantly different, but the difference was insignificant in the ASP group; no significant difference was shown in both groups in levels of triglyceride, total cholesterol and very low density lipoprotein-cholesterol. **CONCLUSION:** PNS may inhibit activation of platelet through multiple components and multiple pathways, which is different from that of ASP, only through inhibition on arachidonic acid metabolism to suppress platelet aggregation. PNS has effects of decreasing platelet superficial activation, inhibiting platelet adhesion and aggregation, preventing thrombosis and improving microcirculation, and its therapeutic effect on clinical syndrome is better than that of ASP.

### Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial.

Brooks WA, Yunus M, Santosham M, et al. *Lancet* 2004;363:1683-1688.

**BACKGROUND:** Pneumonia is a leading cause of morbidity and mortality in young children. Early reversal of severity signs – chest indrawing, hypoxia, and tachypnoea – improves outcome. We postulated that zinc, an acute phase reactant, would shorten duration of severe pneumonia and time in hospital. **METHODS:** In a double-blind placebo-controlled clinical trial in Matlab Hospital, Bangladesh, 270 children aged 2-23 months were randomised to receive elemental zinc (20 mg per day) or placebo, plus the hospital's standard antimicrobial management, until discharge. The outcomes were time to cessation of severe pneumonia (no chest indrawing, respiratory rate 50 per min or less, oxygen saturation at least 95% on room air) and discharge from hospital. Discharge was allowed when respiratory rate was 40 per minute or less for 24 consecutive hours while patients were maintained only on oral antibiotics. **FINDINGS:** The group receiving zinc had reduced duration of severe pneumonia (relative hazard [RH]=0.70, 95% CI 0.51-0.98), including duration of chest indrawing (0.80, 0.61-1.05), respiratory rate more than 50 per min (0.74, 0.57-0.98), and hypoxia (0.79, 0.61-1.04), and overall hospital duration (0.75, 0.57-0.99). The mean reduction is equivalent to 1 hospital day for both severe pneumonia and time in hospital. All effects were greater when children with wheezing were omitted from the analysis. **INTERPRETATION:** Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children, and could help reduce antimicrobial resistance by decreasing multiple antibiotic exposures, and lessen complications and deaths where second line drugs are unavailable.

### Effects of inositol on ovarian function and metabolic factors in women with PCOS: a randomized double blind placebo-controlled trial.

Gerli S, Mignosa M, Di Renzo GC.  
*Eur Rev Med Pharmacol Sci*  
2003;7:151-159.

**BACKGROUND:** Women with oligomenorrhea and polycystic ovaries show a high incidence of ovulation failure perhaps linked to insulin resistance and related metabolic features. A small number of reports show that inositol improves ovarian function. Furthermore, in these trials the quality of evidence supporting ovulation is suboptimal, and few studies have been placebo-controlled. The aim of this study was to use a double-blind, placebo-controlled approach with detailed assessment of ovarian activity (two blood samples per week) to assess the validity of this therapeutic approach in this group of women. **METHODS:** Of the 283 patients randomized, 2 withdrew before treatment commenced, 147 received placebo, and 136 received inositol (100 mg, twice a day). The women who discontinued the study prematurely were more numerous in the treatment group (n = 45) than the placebo group (n = 15; P < 0.05). **RESULTS:** The ovulation frequency estimated by the ratio of luteal phase weeks to observation weeks was significantly (P < 0.01) higher in the treated group (23%) compared with the placebo (13%). The time in which the first ovulation occurred was significantly (P < 0.05) shorter [23.6 d; 95% confidence interval (CI), 17, 30; compared with 41.8 d; 95% CI, 28, 56]. The number of patients failing to ovulate during the placebo-treatment period was higher (P < 0.05) in the placebo group, and in most cases ovulations were characterized by normal progesterone concentrations in both groups. The effect of inositol on follicular maturation was rapid, because the circulating concentration of E2 increased only in the inositol group during the first week of treatment. Significant (P < 0.01) weight loss (and leptin reduction) was recorded in the inositol group, whereas in the placebo group was recorded an increase of the weight (P < 0.05). A significant increase in circulating high-density lipoprotein was

observed only in the inositol-treated group. Metabolic risk factor benefits of inositol treatment were not observed in the morbidly obese subgroup of patients (body mass index > 37). No change in fasting glucose concentrations, fasting insulin, or insulin responses to glucose challenge test was recorded after 14-wk of inositol and placebo therapy. There was an inverse relationship between body mass of the patients and the efficacy of the treatment. **CONCLUSIONS:** These data support a beneficial effect of inositol in improving ovarian function in women with oligomenorrhea and polycystic ovaries.

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### Plasma antioxidative activity in patients with pulmonary tuberculosis.

Kowalski J, Janiszewska-Drobinska B, Pawlicki L, et al. *Pol Merkuriusz Lek* 2004;16:119-122. [Article in Polish]

Plasma antioxidative activity was determined by spectrophotometric method by estimation of plasma volume resulting in inhibition of free radical reaction rate by 50%. The study comprised 40 patients with pulmonary tuberculosis (25 men, 15 women) aged 19-77 years (mean 48.5). Every patient had infiltrative pulmonary tuberculosis diagnosed. After 1-month therapy with tuberculostatic drugs vitamins C and E were added in 15 patients in a daily dose of 1.0 g and 600 mg respectively. The control group consisted of 16 clinically healthy subjects (12 men, 4 women) aged 28-57 years (mean 42.5). Decrease in plasma antioxidative activity was found in patients as compared to the controls before as well as after therapy with tuberculostatic drugs. However, in patients with added vitamins (after 1-month tuberculostatic therapy) increase in plasma antioxidant activity was observed.

**The effect of inositol supplements on the psoriasis of patients taking lithium: a randomized, placebo-controlled trial.**

Allan SJ, Kavanagh GM, Herd RM, Savin JA. *Br J Dermatol* 2004;150:966-999.

**BACKGROUND:** Lithium carbonate is the most widely used long-term treatment for bipolar affective disorders, but its ability to trigger and exacerbate psoriasis can become a major problem in patients for whom lithium is the only treatment option. Inositol depletion underlies the action of lithium in bipolar affective disorders and there are good theoretical reasons why the use of inositol supplements might be expected to help this group of patients. **OBJECTIVES:** To determine whether inositol supplements improve the psoriasis of patients on lithium therapy. **METHODS:** Fifteen patients with psoriasis, who were taking lithium, took part in a randomized, double-blind, placebo-controlled, crossover clinical trial comparing the effect of inositol supplements with those of a placebo (lactose). Changes in the severity of their psoriasis were measured by Psoriasis Area and Severity Index scores recorded before and after the different courses of treatment. The effect of inositol supplements on the psoriasis of 11 patients who were not taking lithium was evaluated in the same way. **RESULTS:** The inositol supplements had a significantly beneficial effect on the psoriasis of patients taking lithium. No such effect was detected on the psoriasis of patients not on lithium. **CONCLUSIONS:** The use of inositol supplements is worth considering for patients with intractable psoriasis who need to continue to take lithium for bipolar affective disorders.

**Treatment with all-trans retinoic acid plus tamoxifen and vitamin E in advanced hepatocellular carcinoma.**

Clerici C, Castellani D, Russo G, et al. *Anticancer Res* 2004;24:1255-1260.

**BACKGROUND:** Low serum retinol and hepatic tocopherol levels correlate with hepatocellular carcinoma (HCC) risk. Antiestrogen tamoxifen seems useful in HCC patients. A pilot study was performed to evaluate the effect of all-trans retinoic acid associated with tamoxifen and vitamin E on patients with advanced HCC. **PATIENTS AND METHODS:** Fifteen consecutive patients with advanced HCC were included in the study. Patients were evaluated for survival, quality of life, liver function, tumor mass, toxicity related to the treatment and retinoid receptors in liver biopsies. **RESULTS:** The median survival of our patients was 22 months. Pain and asthenia were improved in the majority of patients. Every patient with baseline elevated liver enzymes showed an improvement in liver function. RAR-alpha, RXR-alpha, RAR-beta and RAR-gamma receptors were demonstrated in 100%, 73%, 47% and 40%, respectively. **CONCLUSION:** A combination therapy of all-trans retinoic acid, tamoxifen and vitamin E increases the survival rate and ameliorates the clinical outcome in patients with inoperable HCC.

### **A randomized trial of nicotinamide and vitamin E in children with recent onset type 1 diabetes (IMDIAB IX).**

Crino A, Schiaffini R, Manfrini S, et al. *Eur J Endocrinol* 2004;150:719-724.

**OBJECTIVE:** Various adjuvant therapies have been introduced along with intensive insulin therapy in patients with recent onset type 1 diabetes. Nicotinamide (NA), administered at diagnosis of the disease, can have beneficial effects on the clinical remission rate, improve metabolic control and preserve or slightly increase beta-cell function, probably by reducing toxicity due to free oxygen radicals. Vitamin E, a known antioxidant, inhibits lipid peroxidation; this can lead to protection of islet beta cells from the combined effects of interleukin 1, tumor necrosis factor and gamma interferon. The aim of the present study was to investigate whether the addition of vitamin E to NA could improve metabolic control and the residual beta-cell function, as measured by C-peptide secretion, in children and adolescents with recent onset type 1 diabetes; patients were followed-up for 2 years after diagnosis. **PATIENTS AND STUDY DESIGN:** Recent onset type 1 diabetes patients (n=64, mean age 8.8 years) were recruited by participating centres of the IMDIAB group. Thirty-two patients were randomized to NA (25 mg/kg body weight) plus vitamin E (15 mg/kg body weight); 32 patients acted as controls and received NA only at the same dose as above. Intensive insulin therapy was applied to both treatment groups. **RESULTS:** There were three drop outs during the 2-year follow-up period. Overall, patients assigned to the NA+vitamin E group or the NA group did not significantly differ in terms of glycosylated hemoglobin (HbA1c) levels, insulin requirement or baseline C-peptide secretion. Patients diagnosed at an age of less than 9 years showed significantly reduced C-peptide levels compared with those aged over 9 years at diagnosis and at the 2-year follow-up but there were no differences between the NA and NA+vitamin E treated groups. However at 6 months, patients over 9 years of age treated with NA+vitamin E showed significantly higher C-peptide compared with the NA group

( $P < 0.003$ ). In both age groups and in the different treatment groups, C-peptide levels found at diagnosis were preserved 2 years later. **CONCLUSIONS:** The use of NA alone, or in combination with vitamin E, along with intensive insulin therapy is able to preserve baseline C-peptide secretion for up to 2 years after diagnosis. This finding is of particular interest for pre-pubertal children with type 1 diabetes and has never been reported before.

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### **Immediate effects of n-3 fatty acid infusion on the induction of sustained ventricular tachycardia.**

Schrepf R, Limmert T, Claus Weber P, et al. *Lancet* 2004;363:1441-1442.

Increased consumption of n-3 fatty acids reduces mortality from sudden cardiac death, indicating that such acids have anti-arrhythmic effects. We did electrophysiological testing in ten patients with implanted cardioverter defibrillators who were at high risk of sudden cardiac death. To assess their immediate effects on the induction of sustained ventricular tachycardia, n-3 fatty acids were infused. Such tachycardia was not induced in five of seven patients. Our findings show that infusion of n-3 polyunsaturated fatty acids does not induce arrhythmia, but did result in a reduction of sustained ventricular tachycardia in some patients.

**Double-masked, placebo-controlled, randomized trial of lutein and antioxidant supplementation in the intervention of atrophic age-related macular degeneration: the Veterans LAST study (Lutein Antioxidant Supplementation Trial).**

Richer S, Stiles W, Statkute L, et al. *Optometry* 2004;75:216-230.

**BACKGROUND:** Age-related macular degeneration (ARMD) is the leading cause of vision loss in aging Western societies. The objective of the lutein antioxidant supplementation trial (LAST) is to determine whether nutritional supplementation with lutein or lutein together with antioxidants, vitamins, and minerals, improves visual function and symptoms in atrophic ARMD. **METHODS:** The study was a prospective, 12-month, randomized, double-masked, placebo-controlled trial conducted at an urban midwestern Veterans Administration Hospital from August 1999 to May 2001. Ninety patients with atrophic ARMD were referred by ophthalmologists at two Chicago-area veterans medical facilities. Patients in Group 1 received lutein 10 mg (L); in Group 2, a lutein 10 mg/antioxidants/vitamins and minerals broad spectrum supplementation formula (L/A); and in Group 3, a maltodextrin placebo (P) over 12 months. **RESULTS:** In Groups 1 L and 2 L/A, mean eye macular pigment optical density increased approximately 0.09 log units from baseline, Snellen equivalent visual acuity improved 5.4 letters for Group 1 L and 3.5 letters for Group 2 L/A, and contrast sensitivity improved. There was a net subjective improvement in Amsler grid in Group 1 L. VFO-14 questionnaires concerning subjective glare recovery were nearly significant at 4 months for Group 2 L/A. Patients who received the placebo (Group 3) had no significant changes in any of the measured findings. **CONCLUSION:** In this study, visual function is improved with lutein alone or lutein together with other nutrients. Further studies are needed with more patients, of both genders, and for longer periods of time to assess long-term effects of lutein or lutein together with a broad spectrum of antioxidants, vitamins, and minerals in the treatment of atrophic age-related macular degeneration.

**Antioxidant diet supplementation influences blood iron status in endurance athletes.**

Aguilo A, Tauler P, Fuentespina E, et al. *Int J Sport Nutr Exerc Metab* 2004;14:147-160.

**OBJECTIVE:** The aim of this work was to check the effects of antioxidant supplementation (vitamins E and C, and beta-carotene) on the basal iron status of athletes prior to and following their training and competition season (3 months). **DESIGN:** Eighteen amateur trained male athletes were randomly distributed in 2 groups: placebo (lactose) and antioxidant supplemented (vitamin E, 500 mg/d; vitamin C, 1 g/d; and beta-carotene, 30 mg/d). The study was double blind. Hematological parameters, dietary intake, physical activity intensity, antioxidant status (GSH/GSSG ratio), and basal iron status (serum iron, transferrin, ferritin, and iron saturation index) were determined before and after the intervention trials. **RESULTS:** Exercise decreased antioxidant defenses in the placebo group but not in the antioxidant-supplemented group. No changes were found in the number of erythrocytes, hematocrit, or hemoglobin concentration, or in values of serum iron parameters, after taking the antioxidant cocktail for 3 months, in spite of the exercise completed. The placebo group showed a high oxidative stress index, and decreases in serum iron (24%) and iron saturation index (28%), which can neither be attributed to aspects of the athletes' usual diet, nor to hemoconcentration. **CONCLUSIONS:** Antioxidant supplementation prevents the decrease of serum iron and the iron saturation index, and a link between iron metabolism and oxidative stress may also be suggested.

### **Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial.**

Yale SH, Liu K. *Arch Intern Med* 2004;164:1237-1241.

**BACKGROUND:** Echinacea purpurea stimulates the immune response and is promoted to reduce symptom severity and the duration of upper respiratory tract infections. We sought to determine the efficacy of a standardized preparation of E purpurea in reducing symptom severity and duration of the common cold. **METHODS:** A randomized, double-blind, placebo-controlled design was used. Patients received either 100 mg of E purpurea (freeze-dried pressed juice from the aerial portion of the plant) or a lactose placebo 3 times daily until cold symptoms were relieved or until the end of 14 days, whichever came first. Symptoms (sneezing, nasal discharge, nasal congestion, headache, sore or scratchy throat, hoarseness, muscle aches, and cough) were scored subjectively by the patient and recorded daily in a diary. Kaplan-Meier curves were used to estimate the survival function of time to resolution in each group. The Wilcoxon rank sum test was used to compare time to resolution between the 2 groups. **RESULTS:** One hundred twenty-eight patients were enrolled within 24 hours of cold symptom onset. Group demographic distribution was comparable for sex, age, time from symptom onset to enrollment in the study, average number of colds per year, and smoking history. No statistically significant difference was observed between treatment groups for either total symptom scores (P range, .29-.90) or mean individual symptom scores (P range, .09-.93). The time to resolution of symptoms was not statistically different (P = .73). **CONCLUSIONS:** Some studies have concluded that Echinacea effectively reduces the symptoms and duration of the common cold. We were unable to replicate such findings. Further studies using different preparations and dosages of E purpurea are necessary to validate previous claims.

### **A prospective study of plasma selenium levels and prostate cancer risk.**

Li H, Stampfer MJ, Giovannucci EL, et al. *J Natl Cancer Inst* 2004;96:696-703.

**BACKGROUND:** Epidemiologic studies suggest that low selenium levels are associated with an increased incidence of prostate cancer, although results are conflicting. We examined the association between pre-diagnostic plasma selenium levels and risk of prostate cancer in men enrolled in the Physicians' Health Study. **METHODS:** Using plasma samples obtained in 1982 from healthy men enrolled in the study, we conducted a nested case-control study among 586 men diagnosed with prostate cancer during 13 years of follow-up and 577 control subjects. Odds ratios (ORs) and 95% confidence intervals (CIs) for the risk of prostate cancer in pre- (before October 1990) and post- (after October 1990) prostate-specific antigen (PSA) screening eras were calculated using multivariable logistic regression. **RESULTS:** Pre-diagnostic plasma selenium levels were inversely associated with risk of advanced prostate cancer (5th versus 1st quintile OR = 0.52, 95% CI = 0.28 to 0.98; P(trend) = .05), even among men diagnosed after 1990 (5th versus 1st quintile OR = 0.39, 95% CI = 0.16 to 0.97). The inverse association with prostate cancer risk was observed only for case subjects with elevated baseline PSA levels (PSA >4 ng/mL, 5th versus 1st quintile OR = 0.49, 95% CI = 0.28 to 0.86; P(trend) = .002). These inverse associations were observed in both pre- and post-PSA eras. **CONCLUSIONS:** The inverse association between baseline plasma selenium levels and risk of advanced prostate cancer, even among men diagnosed during the post-PSA era, suggests that higher levels of selenium may slow prostate cancer tumor progression. Ongoing randomized trials of selenium supplements may help to further evaluate this issue.

### Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial.

Esposito K, Giugliano F, Di Palo C, et al. *JAMA* 2004;29:2978-2984.

**CONTEXT:** Healthy lifestyle factors are associated with maintenance of erectile function in men. **OBJECTIVE:** To determine the effect of weight loss and increased physical activity on erectile and endothelial functions in obese men. **DESIGN, SETTING, AND PATIENTS:** Randomized, single-blind trial of 110 obese men (body mass index  $>$  or  $=30$ ) aged 35 to 55 years, without diabetes, hypertension, or hyperlipidemia, who had erectile dysfunction that was determined by having a score of 21 or less on the International Index of Erectile Function (IIEF). The study was conducted from October 2000 to October 2003 at a university hospital in Italy. **INTERVENTIONS:** The 55 men randomly assigned to the intervention group received detailed advice about how to achieve a loss of 10% or more in their total body weight by reducing caloric intake and increasing their level of physical activity. Men in the control group ( $n = 55$ ) were given general information about healthy food choices and exercise. **MAIN OUTCOMES MEASURES:** Erectile function score, levels of cholesterol and triglycerides, circulating levels of interleukin 6, interleukin 8, and C-reactive protein, and endothelial function as assessed by vascular responses to L-arginine. **RESULTS:** After 2 years, body mass index decreased more in the intervention group (from a mean [SD] of 36.9 [2.5] to 31.2 [2.1]) than in the control group (from 36.4 [2.3] to 35.7 [2.5]) ( $P < .001$ ), as did serum concentrations of interleukin 6 ( $P = .03$ ), and C-reactive protein ( $P = .02$ ). The mean (SD) level of physical activity increased more in the intervention group (from 48 [10] to 195 [36] min/wk;  $P < .001$ ) than in the control group (from 51 [9] to 84 [28] min/wk;  $P < .001$ ). The mean (SD) IIEF score improved in the intervention group (from 13.9 [4.0] to 17 [5];  $P < .001$ ), but remained stable in the control group (from 13.5 [4.0] to 13.6 [4.1];  $P = .89$ ). Seventeen men in the intervention group and 3 in the control group ( $P = .001$ ) reported an IIEF score of 22 or higher. In multivariate analyses, changes in body mass index ( $P = .02$ ), physical activity ( $P = .02$ ), and C-reactive protein ( $P = .03$ ) were independently associated with changes in IIEF score. **CONCLUSION:** Lifestyle changes are associated with improvement in sexual function in about one third of obese men with erectile dysfunction at baseline.

### A placebo-controlled double-blind randomized trial of the use of combined L-carnitine and L-acetyl-carnitine treatment in men with asthenozoospermia.

Lenzi A, Sgro P, Salacone P, et al. *Fertil Steril* 2004;81:1578-1584.

**OBJECTIVE:** To determine the efficacy of combined L-carnitine and L-acetyl-carnitine therapy in infertile males with oligo-astheno-teratozoospermia. **DESIGN:** Placebo-controlled double-blind randomized trial. **SETTING:** University tertiary referral center. **PATIENT(S):** Sixty infertile patients (aged 20-40 years) with the following baseline sperm selection criteria: concentration, 10 to 40  $\times 10^6$ /mL; forward motility,  $<15\%$ ; total motility, 10% to 40%; and atypical forms,  $<80\%$ . Fifty-six patients completed the study. **INTERVENTION(S):** Patients were submitted to a combined treatment of L-carnitine (2 g/d) and L-acetyl-carnitine (1 g/d) or of placebo; the study design was 2 months' wash-out, 6 months of therapy or of placebo, and 2 months' follow-up. **MAIN OUTCOME MEASURE(S):** Variation in the semen parameters that were used for patient selection. **RESULT(S):** Even though increases were seen in all sperm parameters after combined carnitine treatment, the most significant improvement in sperm motility (both forward and total) was present in patients who had lower initial absolute values of motile sperm ( $<4 \times 10^6$  forward or  $<5 \times 10^6$  total motile spermatozoa per ejaculate). **CONCLUSION(S):** Combined treatment with L-carnitine and L-acetyl-carnitine in a controlled study of efficacy was effective in increasing sperm motility, especially in groups with lower baseline levels.

### **The effects of potassium and magnesium supplementations on urinary risk factors of renal stone patients.**

Jaipakdee S, Prasongwatana V, Premgamone A, et al.

*J Med Assoc Thai* 2004;87:255-263.

The effects of potassium and magnesium supplementation on urinary risk factors for renal stone disease were studied in 61 renal stone patients. The subjects were divided into four groups and supplemented for a period of one month with potassium chloride (KCl, Group 1), potassium sodium citrate (K Na citrate, Group 2), magnesium glycine (Mg glycine, Group 3) and potassium magnesium citrate (K Mg citrate, Group 4) with a daily dose of 42 mEq potassium, 21 mEq magnesium or sodium and 63 mEq citrate, accordingly. The results showed that serum potassium and magnesium of all four groups normalized after the supplementation. Though urinary potassium significantly increased in all three groups supplemented with elemental potassium containing solutions [i.e. KCl ( $p < 0.001$ ), K Na citrate ( $p < 0.001$ ) and K Mg citrate ( $p < 0.001$ )] only K Na citrate and K Mg citrate, caused a significant increase in urinary pH and citrate but decrease in calcium. Supplementation with Mg glycine in Group 3 although caused a significant increase in urinary magnesium, its effects on urinary pH, citrate and calcium, however, were similar to KCl, in that they caused a significant decrease in urinary pH without any change in urinary citrate or calcium. Supplementation with K Mg citrate in Group 4 seems to have given the best results, as far as lowering stone risk factors in that it caused an increase in urinary pH, potassium and citrate and decreased calcium excretions similar to K Na citrate in Group 2. In addition, K Mg citrate also caused the enrichment of urine with magnesium, another inhibitor of calcium-containing stones. Although the four supplements had no effect on urinary saturation of calcium oxalate salt, their effects on the saturations of brushite ( $\text{CaHPO}_4 \times 2\text{H}_2\text{O}$ ), octacalcium phosphate ( $\text{Ca}_8\text{H}_2(\text{PO}_4)_6 \times 5\text{H}_2\text{O}$ ) and uric acid were clearly associated with changes in urinary pH. Therefore, in Group 1 and 3, subjects having a decrease in urinary pH, also experienced a significant increase in uric acid saturation. Though the saturation of brushite and

octacalcium phosphate in Group 2 and 4 and the sodium acid urate in Group 2 were significantly increased, these urinary risk factors could be overcome, however, by the concomitant increase in urinary citrate. The present results demonstrate that for those stone vulnerable subjects having a high risk of potassium and magnesium depletion, to obtain the best therapeutic results, they should be provided supplementations of both potassium and magnesium together and also in the forms that would result in the delivery of an alkali loading effect.

### **Lysine fortification reduces anxiety and lessens stress in family members in economically weak communities in northwest Syria.**

Smriga M, Ghosh S, Mouneimne Y, et al. *Proc Natl Acad Sci U S A* 2004;101:8285-8288.

Lysine is a limiting amino acid in diets based on wheat as the staple. In experimental animals, prolonged dietary lysine inadequacy increases stress-induced anxiety. If observed in humans, such a result would have a strong implication for the relationship between nutrition and communal quality of life and mental health. As part of a 3-month randomized double-blind study, we tested whether lysine fortification of wheat reduces anxiety and stress response in family members in poor Syrian communities consuming wheat as a staple food. In the lysine-fortified group, the plasma cortisol response to the blood drawing as a cause of stress was reduced in females, as was sympathetic arousal in males as measured by skin conductance. Lysine fortification also significantly reduced chronic anxiety as measured by the trait anxiety inventory in males. These results suggest that some stress responses in economically weak populations consuming cereal-based diets can be improved with lysine fortification

**Lutein, zeaxanthin, macular pigment, and visual function in adult cystic fibrosis patients.**

Schupp C, Olano-Martin E, Gerth C, et al. *Am J Clin Nutr* 2004;79:1045-1052.

**BACKGROUND:** Pancreatic insufficiency in cystic fibrosis (CF), even with replacement pancreatic enzyme therapy, is often associated with decreased carotenoid absorption. Because the macular pigment of the retina is largely derived from 2 carotenoids, lutein and zeaxanthin, the decreased serum concentrations seen in CF may have consequences for ocular and retinal health. **OBJECTIVES:** Our aims were to determine plasma carotenoid concentrations, determine absorption and distribution of macular pigment, and assess retinal health and visual function in CF patients. **DESIGN:** In 10 adult CF patients (ages 21-47 y) and 10 age- and sex-matched healthy control subjects, we measured macular pigment density in vivo, measured serum lutein and zeaxanthin concentrations, and comprehensively assessed visual performance (including contrast sensitivity, color discrimination, and retinal function) under conditions of daylight illumination. **RESULTS:** Serum lutein and zeaxanthin were significantly reduced ( $P < 0.005$ ) in CF patients ( $\pm$  SD: 87  $\pm$  36.1 and 27  $\pm$  15.8 nmol/L, respectively) compared with control subjects (190  $\pm$  72.1 and 75  $\pm$  23.6 nmol/L, respectively). Although macular pigment optical density was significantly lower ( $P < 0.0001$ ) in the CF group (0.24  $\pm$  0.11) than in the control group (0.53  $\pm$  0.12), no significant differences in visual function were observed. **CONCLUSIONS:** Adults with CF have dramatically low serum and macular concentrations of carotenoids (lutein and zeaxanthin), but their ocular status and visual function are surprisingly good. The clinical implications of low plasma concentrations of carotenoids in CF are yet to be clarified.

**Effect of age on plasma homocysteine concentrations in young and elderly subjects considering serum vitamin concentrations and different lifestyle factors.**

Strassburg A, Krems C, Luhrmann PM, et al. *Int J Vitam Nutr Res* 2004;74:129-136.

**OBJECTIVES:** The aim of this study was to investigate whether an increase in total homocysteine (tHcy) concentration with increasing age is due to diminishing serum concentrations of pyridoxal-5-phosphate (PLP), vitamin B-12, and folate. The possible influence of different lifestyle factors on tHcy concentration was considered. **METHODS:** Plasma tHcy, serum concentrations of pyridoxal-5-phosphate, vitamin B-12, and folate, intake of coffee and tea, alcohol, and methionine, as well as cigarette smoking, were determined in 252 elderly subjects (60-87 years old) of the longitudinal study on nutrition and health status in an aging population in Giessen (GISELA) and 99 young adults (20-34 years old) of the study on health and nutrition of young adults (GEJE). **RESULTS:** Mean plasma tHcy concentrations were significantly higher in elderly than in young female subjects (9.7  $\pm$  1.9 micromol/L vs. 9.0  $\pm$  1.6 micromol/L,  $p < 0.05$ ), but there was no difference between elderly and young men (10.6  $\pm$  2.1 micromol/L vs. 10.7  $\pm$  2.6 micromol/L). No differences in tHcy were observed between young and elderly subjects after adjustment for serum concentrations of PLP, vitamin B-12, and folate. Multiple linear regression analysis revealed a significant influence of age only in elderly, but not in younger subjects. **CONCLUSION:** Higher tHcy concentrations in the elderly, in comparison to younger women, are due to lower serum concentrations of PLP, vitamin B-12, and folate, whereas within the age group of elderly subjects alone tHcy concentrations increase with age irrespective of serum vitamin concentrations.

### **The effects of Ginkgo biloba extract (LI 1370) supplementation and discontinuation on activities of daily living and mood in free living older volunteers.**

Trick L, Boyle J, Hindmarch I.  
*Phytother Res* 2004;18:531-537.

The aim of the study was to investigate the effects of continuing treatment with Ginkgo biloba extract (GBE) 120 mg/day on the activities of daily living (ADLs) and mood in healthy older volunteers who had immediately previously participated in a survey of the effects of a 4 month treatment with the drug. Following a prior postal survey investigating the effects of 4 months supplementation with GBE on ADLs and various aspects of mood and sleep, 1570 volunteers continued onto a 6 month follow-up postal survey. Subjects selected their own treatment option for the follow-up survey, which effectively created four groups: a continuation group who received GBE in the initial 4 month study and during the 6 month follow-up (GBE-GBE), a discontinuation group who received GBE in the initial study but not during the follow-up (GBE-NT), a new treatment group who did not receive GBE in the initial 4 month study but who did receive GBE during the 6 month follow-up (NT-GBE), and a no treatment group who received no treatment in either survey (NT-NT). At the end of the 6 month follow-up period each subject completed a line analogue rating scale (LARS) and a self-rating activities of daily living scale (SR-ADL). There were significant differences in the mean overall LARS and SR-ADL scores between the four treatment combination groups at the end of the follow-up period. A factor analysis of the LARS revealed two factors, 'mood' and 'alertness'. When scores from each of the treatment groups were examined over the whole 10 month period it was evident that the ratings of overall competence in the SR-ADL and both factors of the LARS were diminished on cessation of treatment with GBE, and improved when GBE treatment was initiated. The magnitude of the improvements on all scales was related to the overall duration of GBE supplementation. Significant differences between the groups of subjects treated with GBE for different periods of time (4-10 months) suggests that the extract has a demonstrable effect in improving mood and the self-assessed performance of the tasks of everyday living.

### **Combined effects of multiple flavonoids on breast cancer resistance protein (ABCG2)-mediated transport.**

Zhang S, Yang X, Morris ME. *Pharm Res* 2004;21:1263-1273.

**PURPOSE:** The purpose of this study was to determine the dynamic parameter (EC<sub>50</sub>) of flavonoids apigenin, biochanin A, chrysin, genistein, kaempferol, hesperetin, naringenin, and silymarin for breast cancer resistance protein (BCRP) inhibition when used alone, and to evaluate their potential interactions (additive, synergistic, or antagonistic) with regards to BCRP inhibition when used in multiple-flavonoid combinations. **METHODS:** The effects of flavonoids on BCRP-mediated transport were examined by evaluating their effects on mitoxantrone accumulation and cytotoxicity in MCF-7 MX100 cells overexpressing BCRP. The EC<sub>50</sub> values of these flavonoids for increasing mitoxantrone accumulation were estimated using a Hill equation. The potential interactions among multiple flavonoids with regard to BCRP inhibition were assessed by isobologram and Berenbaum's interaction index methods. **RESULTS:** The EC<sub>50</sub> values of these flavonoids for increasing mitoxantrone accumulation ranged from 0.39±0.13 microM to 33.7±2.78 microM. Quantitative analysis of the combined effects of multiple flavonoids on mitoxantrone accumulation indicated that these flavonoids act additively in inhibiting BCRP when given as 2-, 3-, 5-, or 8-flavonoid combinations with equimolar concentrations of all constituents. The results of the mitoxantrone cytotoxicity studies were consistent with these findings. **CONCLUSIONS:** The additive effects of multiple flavonoids for BCRP inhibition suggests that prediction of BCRP-mediated food (herbal product)-drug interactions should also take into consideration the presence of multiple flavonoids and provides a rationale for using "flavonoid cocktails" as a potential approach for multidrug resistance reversal in cancer treatment.